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PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53(c).

Express Mail Label No. EV 394803038 US

INVENTOR(S)

Given Name (first and middle [if any])	Family Name or Surname	Residence (City and either State or Foreign Country)
Chris	Murray	Boulder, Colorado

Additional inventors are being named on the _____ *separately numbered sheets attached hereto*

TITLE OF THE INVENTION (500 characters max)

CRYSTALLINE FORMS OF RSR13 SODIUM SALT

Direct all correspondence to: **CORRESPONDENCE ADDRESS**

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☐ Firm or Individual Name					
Address					
Address					
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Country		Telephone		Fax	

ENCLOSED APPLICATION PARTS *(check all that apply)*

☑ Specification *Number of Pages* 10 ☐ CD(s), Number _____

☑ Drawing(s) *Number of Sheets* 9 ☑ Other (specify) Return Card Receipt

☐ Application Date Sheet. See 37 CFR 1.76

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☑ Applicant claims small entity status. See 37 CFR 1.27.

☑ A check or money order is enclosed to cover the filing fees.

☑ The Director is herby authorized to charge filing fees or credit any overpayment to Deposit Account Number: 19-5117

☐ Payment by credit card. Form PTO-2038 is attached.

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☑ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are: _____

Respectfully submitted,

SIGNATURE _____ Date April 22, 2004

TYPED or PRINTED NAME Darla C. Yoeng REGISTRATION NO. 48,053 *(if appropriate)*

Docket Number: ALL.06/PR

TELEPHONE 303-268-0066

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CRYSTALLINE FORMS OF RSR13 SODIUM SALT

FIELD OF THE INVENTION

[0001] The invention relates to the isolation of crystalline polymorphic forms of RSR13 Sodium Salt (also known as (2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methyl-propionic acid, sodium salt). RSR13 may be used in the treatment of disease, including the treatment of cancers.

BACKGROUND OF THE INVENTION

[0002] The polymorphic behavior of drugs can be of crucial importance in pharmacy and pharmacology. Polymorphs are, by definition, crystals of the same molecule having different physical properties as a result of the order of the molecules in the crystal lattice. When a solvent molecule(s) is contained within the crystal lattice the resulting crystal is called a pseudopolymorph, or solvate. If the solvent molecule(s) within the crystal structure is a water molecule, then the pseudopolymorph/solvate is called a hydrate. The differences in physical properties exhibited by polymorphs affect pharmaceutical parameters such as storage stability, compressibility and density (important in formulation and product manufacturing), and dissolution rates (an important factor in determining bio-availability). (See H. Brittain, Polymorphism in Pharmaceutical Solids, Marcel Dekker, New York, NY, 1999, pp. 1-2). Differences in stability can result from changes in chemical reactivity (e.g. differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph) or mechanical changes (e.g. tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph) or both (e.g. tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in lack of potency or, at the other extreme, toxicity. In addition, the physical properties of the crystal may be important in processing: for example, one polymorph might be more likely to form solvates or might

be difficult to filter and wash free of impurities (i.e particle shape and size distribution might be different between one polymorph relative to the other).

[0003] Polymorphic and pseudopolymorphic forms of the drug substance (also known as the "active pharmaceutical ingredient" (API)), as administered by itself or formulated as a drug product (also known as the final or finished dosage form, or as the pharmaceutical composition) are well known and may affect, for example, the solubility, stability, flowability, fractability, and compressibility of drug substances and the safety and efficacy of drug products, (see, e.g., Knapman, K Modern Drug Discoveries, March 2000: 53).

[0004] The preparation and uses for 2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methyl-propionic acid and its physiologically acceptable salts have been described previously in U.S. Patent Numbers 5,049,695; 5,122,539; 5,290,803; 5,432,191; 5,525,630; 5,648,375; 5,661,182; 5,677,330; 5,705,521; 5,872,888; and 5,927,283, and U.S. Patent Application Publication No. 20030017612 A1. In accordance with the present invention, three crystal forms of RSR13 are provided. These polymorphs, which have been designated as Forms A, B, and C, respectively, are novel crystal forms and are identified hereinbelow.

BRIEF DESCRIPTION OF THE FIGURES

[0005] FIG. 1 is a characteristic X-ray powder diffraction pattern for Form A.

[0006] FIG. 2 is a characteristic X-ray powder diffraction pattern for Form B.

[0007] FIG. 3 is a characteristic X-ray powder diffraction pattern for Form C.

[0008] FIG. 4 is a characteristic differential scanning calorimetry trace for Form A.

[0009] FIG. 5 is a characteristic differential scanning calorimetry trace for Form B.

[0010] FIG. 6 is a characteristic differential scanning calorimetry trace for Form C.

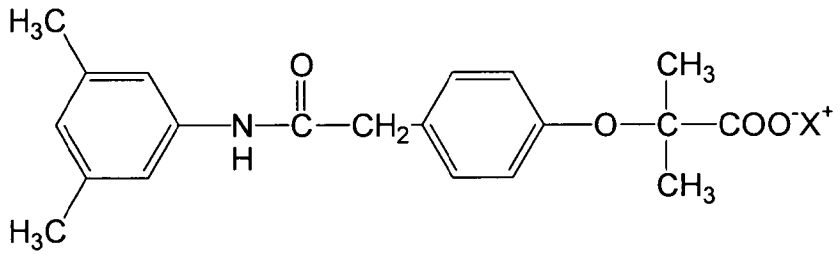
[0011] FIG. 7 is a characteristic FTIR spectrum for Form A.

[0012] FIG. 8 is a characteristic FTIR spectrum for Form B.

[0013] FIG. 9 is a characteristic FTIR spectrum for Form C.

DETAILED DESCRIPTION OF THE INVENTION

[0014] RSR13 2-[4-(((3,5-dimethylanilino)carbonyl)methyl)phenoxy]-2-methylpropionic acid):



is an allosteric effector of hemoglobin, and has been shown to enhance tissue oxygenation *in vivo*. Sometimes, RSR13 is represented by the name 2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methylpropanoic acid. In general RSR13 is administered as a physiologically acceptable salt, such as the monosodium salt; that is, X^+ is Na^+. RSR13 induces allosteric modification of hemoglobin, such that its binding affinity for oxygen is decreased, resulting in increased oxygen distribution to tissues by erythrocytes.

[0015] The ability to allosterically modify hemoglobin also allows the compounds to be useful in treating a variety of disorders and conditions mediated through allosterically modifying hemoglobin to shift oxygen equilibrium in favor of free oxygen. Such disorders may include, but are not limited to, whole body or tissue hypothermia, hypoxia or hypotension, wounds, brain injury, diabetic ulcers, chronic leg ulcers, pressure sores, tissue transplants, stroke or cerebro ischemia, ischemia or oxygen deprivation,

respiratory disorders including acute respiratory distress syndrome and chronic obstructive pulmonary disorder, surgical blood loss, sepsis, multi-system organ failure, normovolemic hemodilution procedures, carbon monoxide poisoning, bypass surgery, carcinogenic tumors, oxygen deprivation of a fetus. The compound is useful in a method comprising the step of administering to a patient suffering from or undergoing the claimed condition a sufficient quantity of an allosteric effector compound. In the case of carcinogenic tumors, the compounds are useful alone, and as radiosensitizers in conjunction with ionizing radiation (See Teicher, (1996) *Drug Dev. Res.* 38:1-11; Rockwell and Kelley (1998) *Rad. Oncol. Invest.* 6:199-208; and Khandelwal et al. (1996) *Rad. Oncol. Invest.* 4:51-59). The allosteric modification properties also allow it to be useful in certain imaging methods, especially blood oxygen level dependent MRI, and also in diagnostic methods, including determination of tumor oxygenation, and determination of an optimal time for commencing radiation treatment based on tumor oxygenation. The preparation and uses for 2-[4-[2-[(3,5-dimethylphenyl)amino]-2-oxoethyl]phenoxy]-2-methyl-propionic acid and its physiologically acceptable salts has been described previously in U.S. Patent Numbers 5,049,695; 5,122,539; 5,290,803; 5,432,191; 5,525,630; 5,648,375; 5,661,182; 5,677,330; 5,705,521; 5,872,888; and 5,927,283, and U.S. Patent Application Publication No. 20030017612 A1. These patents also describe the preparation and use of structurally similar compounds. Other patents describing closely related compounds include 5,248,785; 5,731,454. These patents, applications, and all other patents, applications, and publications referred to herein, are specifically incorporated by reference herein.

[0016] In one aspect, the invention relates to RSR13 in the form of a crystalline solid comprising a first polymorph, denoted Form A. This form is highly crystalline

[0017] In one aspect, the invention relates to RSR13 in the form of a crystalline solid comprising a second polymorph, denoted Form B.

[0018] In one aspect, the invention relates to RSR13 in the form of a crystalline solid comprising a third polymorph, denoted Form C. This form shows peaks at 2-theta values of approximately 9 and 12, similar to those in form B; however, there is a

substantial amount of amorphous material present indicated by broad signals between 2-theta = 15 and 30. These forms showed broad endothermic transitions between 30 and 130°C in their differential scanning calorimetry traces and small exothermic transitions at 130-140°C and 175-184°C, possibly reflecting transitions between different polymorphic forms. In addition, FTIR spectra showed calescence of absorption bands at 1602 and 1558 cm^{-1} which was not observed in the remaining samples. Taken together, these results indicate this represents a distinct crystalline form.

Pharmaceutical Formulations

[0019] For the most effective administration of drug substance of the present invention, it is preferred to prepare a pharmaceutical formulation (also known as the "drug product") preferably in unit dose form, comprising one or more of the RSR13 forms of the present invention and one or more pharmaceutically acceptable carrier, diluent, or excipient. With reference to RSR13, suitable formulations are described in copending U.S. Patent Application Publication No. 20030232887 A1, incorporated by reference herein in its entirety.

[0020] A pharmaceutical formulation may, without being limited by the teachings set forth herein, include a solid form of the present invention which is blended with at least one pharmaceutically acceptable excipient, diluted by an excipient or enclosed within such a carrier that can be in the form of a capsule, sachet, tablet, buccal, lozenge, paper, or other container. When the excipient serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, carrier, or medium for the RSR13 polymorph(s). Thus, the formulations can be in the form of tablets, pills, powders, elixirs, suspensions, emulsions, solutions, syrups, capsules (such as, for example, soft and hard gelatin capsules), suppositories, sterile injectable solutions, and sterile packaged powders.

[0021] Examples of suitable excipients include, but are not limited to, starches, gum arabic, calcium silicate, microcrystalline cellulose, polyvinylpyrrolidone, cellulose, water, syrup, and methyl cellulose. The formulations can additionally include lubricating agents such as, for example, talc, magnesium stearate and mineral oil; wetting agents;

emulsifying and suspending agents; preserving agents such as methyl- and propyl-hydroxybenzoates; sweetening agents; or flavoring agents. Polyols, buffers, and inert fillers may also be used. Examples of polyols include, but are not limited to: mannitol, sorbitol, xylitol, sucrose, maltose, glucose, lactose, dextrose, and the like. Suitable buffers encompass, but are not limited to, phosphate, citrate, tartrate, succinate, and the like. Other inert fillers which may be used encompass those which are known in the art and are useful in the manufacture of various dosage forms. If desired, the solid pharmaceutical compositions may include other components such as bulling agents and/or granulating agents, and the like. The compositions of the invention can be formulated so as to provide quick, sustained, controlled, or delayed release of the drug substance after administration to the patient by employing procedures well known in the art.

[0022] In the event that the above formulations are to be used for parenteral administration, such a formulation typically comprises sterile, aqueous and non-aqueous injection solutions comprising one or more RSR13 forms for which preparations are preferably isotonic with the blood of the intended recipient. These preparations may contain anti-oxidants, buffers, bacteriostats, and solute; which render the formulation isotonic with the blood of the intended recipient. Aqueous and non-aqueous suspensions may include suspending agents and thickening agents. The formulations may be present in unit-dose or multi-dose containers, for example, sealed ampules and vials. Extemporaneous injection solutions and suspensions may be prepared from sterile powders, granules, and tablets of the kind previously described.

[0023] As such, the pharmaceutical formulations of the present invention are preferably prepared in a unit dosage form, each dosage unit containing from about 5 mg to about 200 mg, more usually about 100 mg of the RSR13 form(s). In liquid form, dosage unit contains from about 5 to about 200 mg, more usually about 100 mg of the RSR13 form(s). The term "unit dosage form" refers to physically discrete units suitable as unitary dosages for human subjects/patients or other mammals, each unit containing a predetermined quantity of the RSR13 polymorph calculated to produce the desired

therapeutic effect, in association with preferably, at least one pharmaceutically acceptable carrier, diluent, or excipient.

[0024] The following examples are provided for illustrative purposes only, and are not to be construed as limiting the scope of the claims in any way.

EXAMPLES

Example 1. Preparation of RSR13-Na Polymorph A

[0025] The sodium salt of RSR13 (approximately 325 kg) synthesized as previously described, was diluted with water (1658 L) and the aqueous solution was concentrated under vacuum at a maximum temperature of 50°C to the maximum extraction of solvent, after which absolute ethanol (406 L) was added to provide a mixture having a water content of between 5 and 5.4%. The mixture was then cooled to about 47°C, acetone (975 L) was added and the mixture was stirred while maintaining the temperature. After crystallization, the mixture was stirred for at least one hour, after which an equal volume of acetone was added. The mixture was then slowly cooled to a temperature of about 15°C and stirred for at least 5 hours. The crystals were collected on a filter and washed with acetone (146 L), then dried in a vacuum dryer to a solvent content of less than 1000 ppm acetone and less than 500 ppm ethanol.

Example 2. Preparation of RSR13-Na Polymorph B

[0026] RSR13-Na salt (2.765 kg, 7.61 mole) is added to methanol (4 L), methyl ethyl ketone (MEK) is added (4 L) and the solution is warmed to 40°C. After filtering, more MEK (16 L) is added. The solution is distilled, and additional portions of MEK are added during distillation. The product begins to precipitate out of solution. Acetone (6 L) is added and the mixture is filtered through an 18" Buchner funnel. The isolated RSR13-Na salt is washed several times with acetone, and then dried under vacuum at 70°C for 70 hr. Yield of RSR13-Na salt is 2.72 kg (98.3%)

Example 3. Preparation of RSR13-Na Polymorph C

[0027] RSR13-Na salt (5.572 kg, 15.33 mole) is added to a solution of acetone (20.3 L) and water (2.0 L), and mixture is heated to dissolution and then cooled to approximately 25°C, the mixture is filtered, and the filtrate is cooled to 18°C, a precipitate forms. Acetone can be added to aid stirring. The mixture is filtered, the filter cake is washed with cold acetone and heptane, and then the filter cake is dried in a vacuum oven (50°C) for 48 hr. Yield is 4.075 kg (73.1%).

Example 4. Characterization of RSR13-Na salt Polymorphs A, B, and C using X-ray Diffractometry (XRD)

[0028] XRD patterns were recorded for samples of RSR13-Na on a Philips X'Pert Diffractometer. See Figures 1 – 3 for the XRD patterns of the Polymorphs A, B, and C, respectively.

Example 5. Characterization of RSR13-Na salt Polymorphs A, B, and C using Differential Scanning Calorimetry (DSC)

[0029] DSC traces for samples of RSR13-Na were recorded using a Mettler-Toledo DSC820 system. Each sample was weighed into an aluminium crucible and the crucible crimped and sealed. The crucible + sample was then re-weighed. Each sample was heated from 25-400°C at 5°C/min. After completion of each run when the sample had cooled to ambient temperature, the crucible + sample was re-weighed. The results are listed for the three different polymorphs in the table below. The calorimetry traces are shown in Figures 4-6 for polymorphs A, B, and C, respectively.

RSR13-Na Form XRPD	Area (J/g)	exo 1		exo 2		endo	
		peak (°C)	area (J/g)	peak (°C)	area (J/g)	peak (°C)	area (J/g)
A						249.7	100.9
B						249.9	103.0
C	103.1	131.7	8.5	183.6	14.8	249.4	89.6

[0030] All forms exhibited a sharp endothermic transition at about 250°C which presumably corresponds to the sample melting point. In most samples, this was the only transition detected. Form C showed broad endothermic transitions between 30 and 130°C

in their differential scanning calorimetry traces and small exothermic transitions at 130-140°C and 175-184°C, possibly reflecting transitions between different polymorphic forms.

Example 6. Characterization of RSR13-Na salt Polymorphs A, B, and C using Fourier-Transform Infrared Spectrometry (FT-IR)

[0031] The spectra were recorded on a Perkin Elmer 1600 FTIR spectrometer using diffuse reflectance (KBr disc). See Figures 7-9 for spectra for Polymorphs A, B, and C, respectively.

[0032] The following absorption bands can be distinguished in all three forms:

[0033] 3500-2500 cm^{-1} (broad envelope encompassing NH and CH stretching bands), 1657 cm^{-1} (amide carbonyl stretching), 1602cm^{-1} (carboxylate stretching), 1558 cm^{-1} (amide NH bending), and 1508 cm^{-1} (aromatic C-C). Additionally, Form C shows a coalescence of the absorption bands at 1602 cm^{-1} and 1558 cm^{-1}.

ABSTRACT

There are provided in accordance with the present invention crystalline polymorphs, of a substituted alpha-phenoxy carboxylic acid known as RSR13. Also provided are methods of forming the novel polymorphs, therapeutic methods utilizing them and pharmaceutical dosage forms containing them.

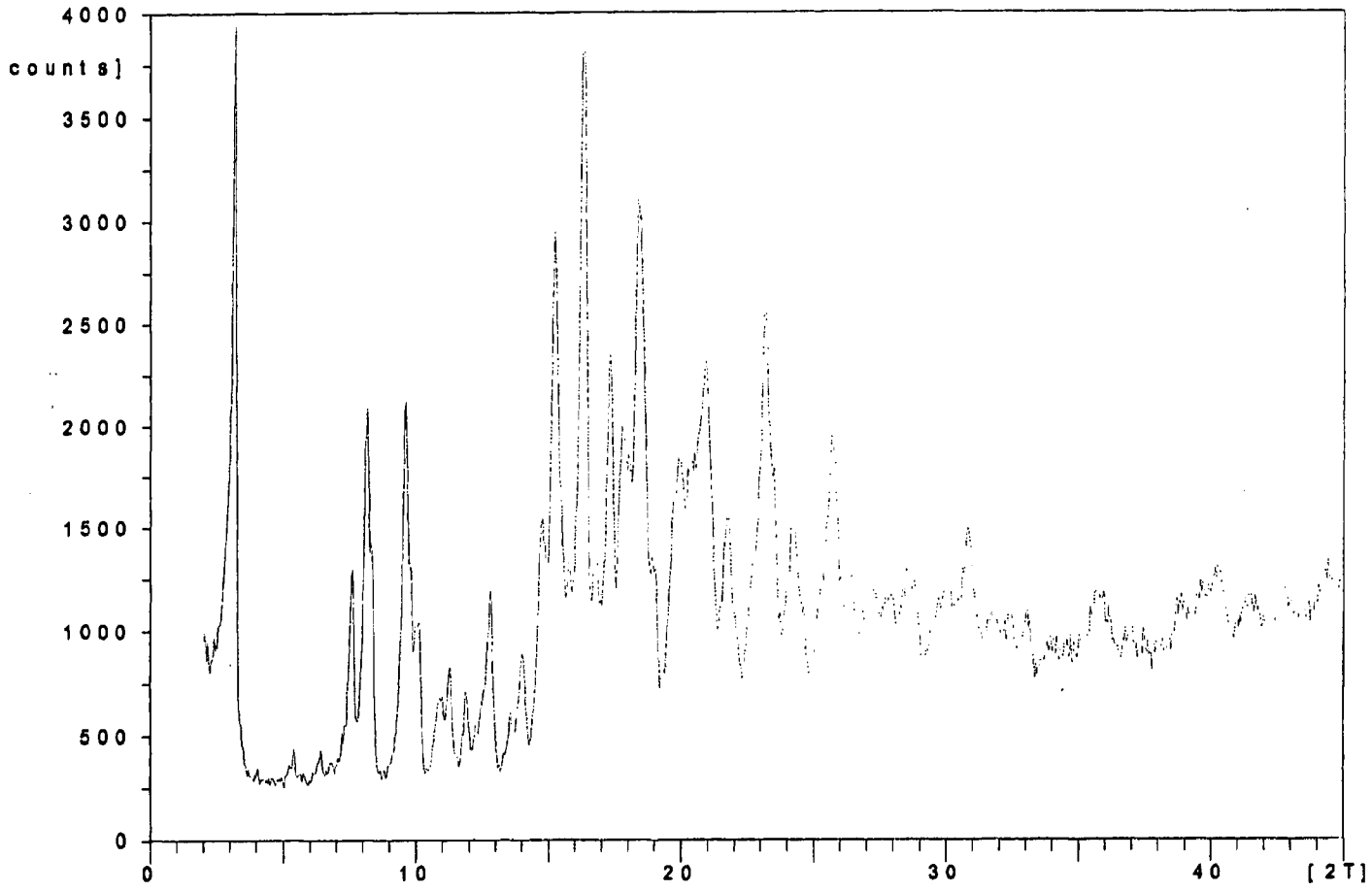


Figure 1

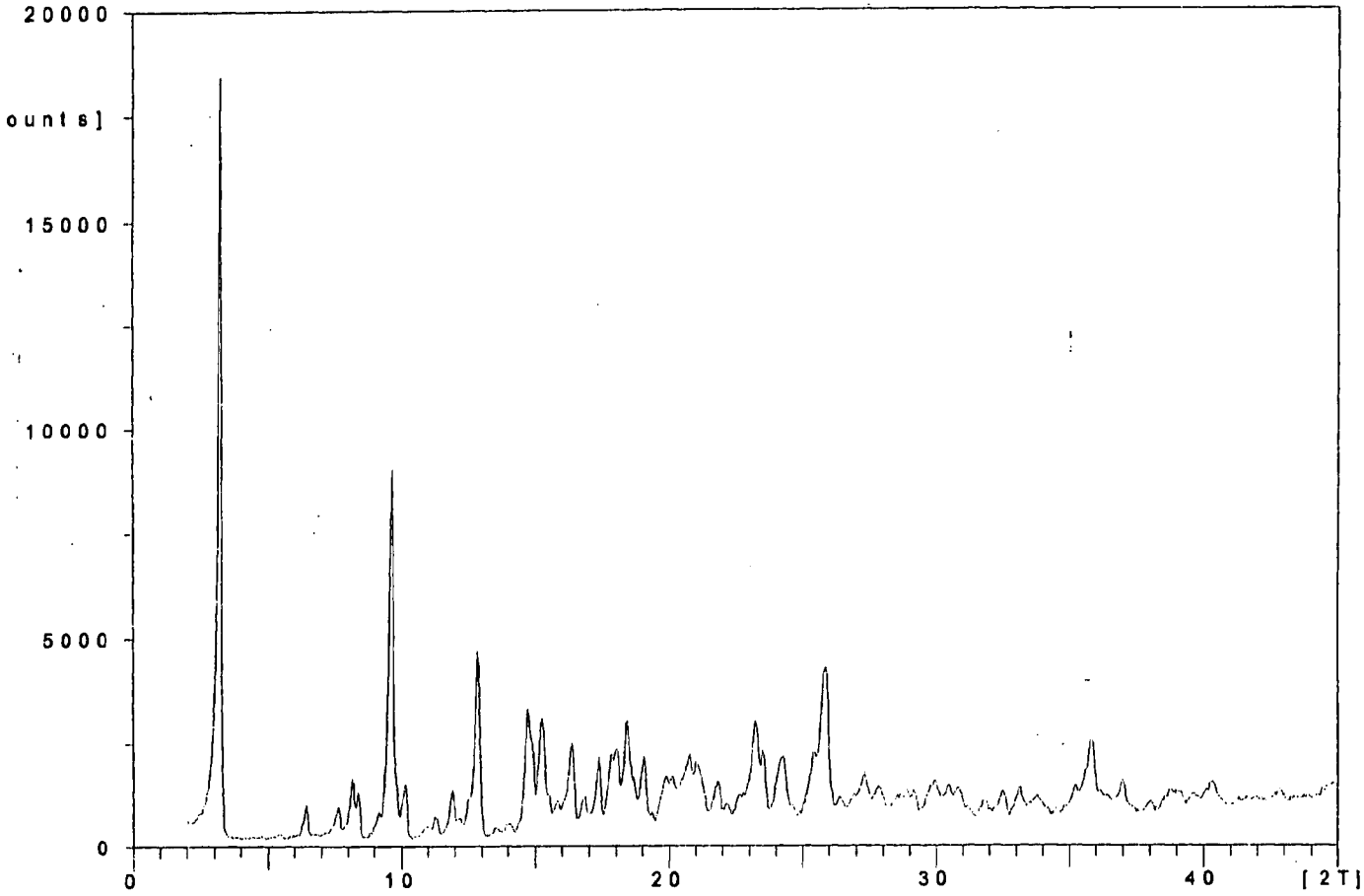


Figure 2

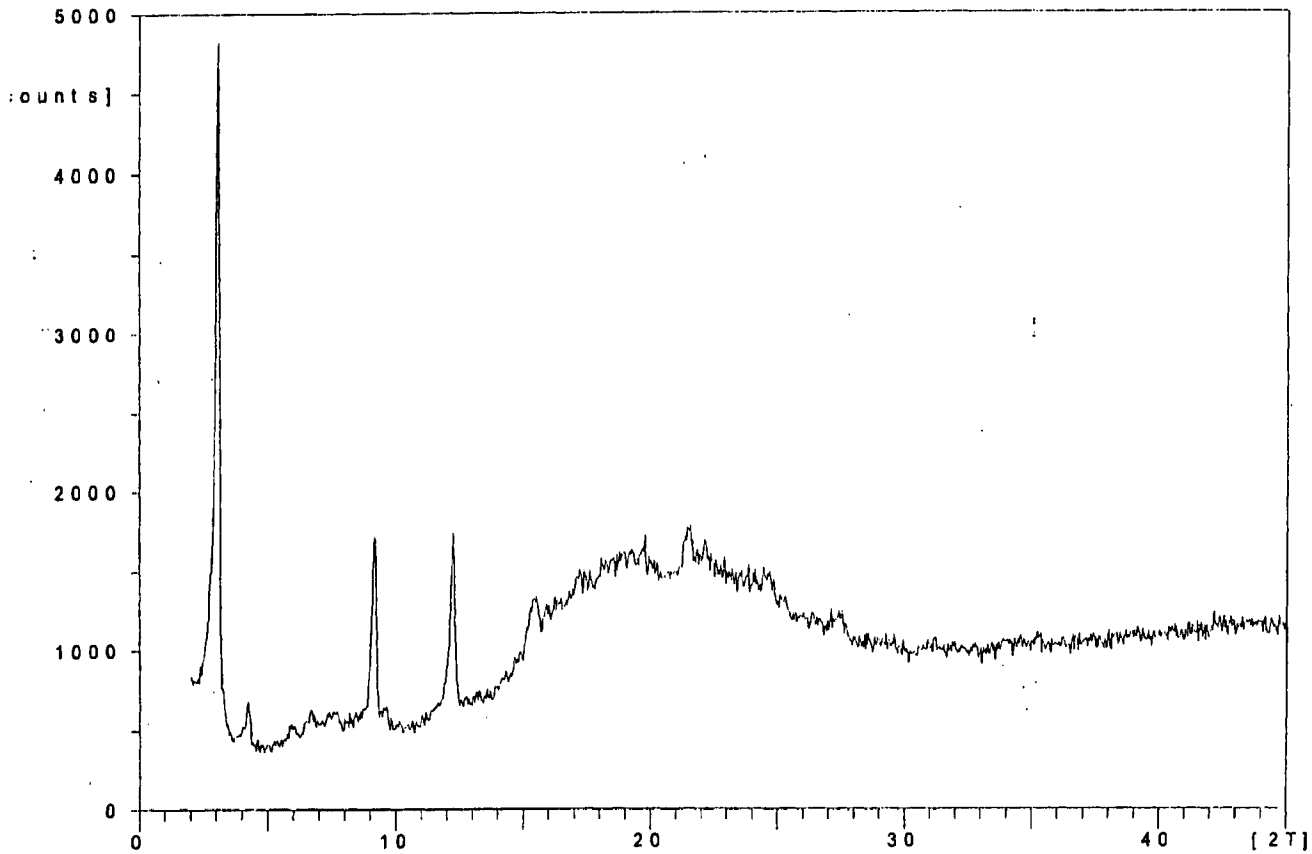
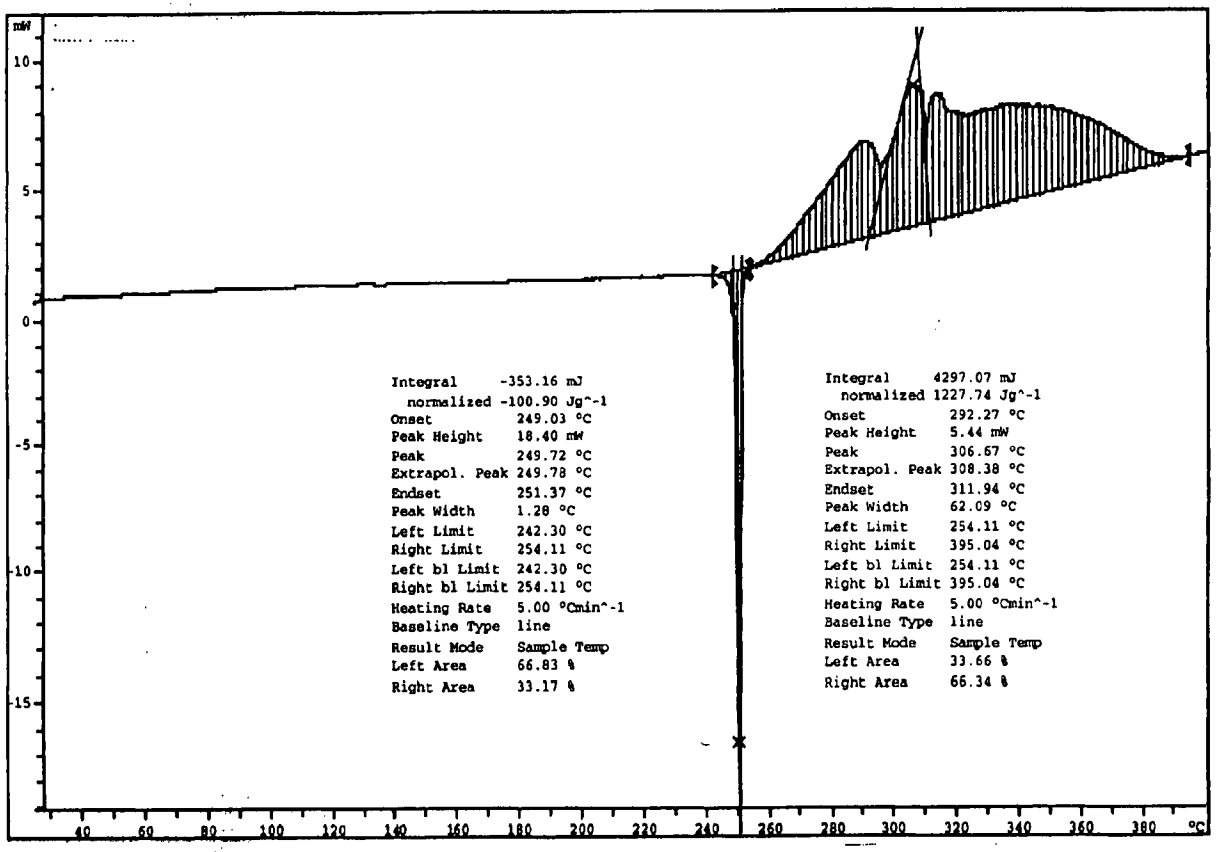


Figure 3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160
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320
340
360
380
°C
Integral -353.16 mJ
normalized -100.90 Jg^-1
Onset 249.03 °C
Peak Height 18.40 mW
Peak 249.72 °C
Extrapol. Peak 249.78 °C
Endset 251.37 °C
Peak Width 1.28 °C
Left Limit 242.30 °C
Right Limit 254.11 °C
Left bl Limit 242.30 °C
Right bl Limit 254.11 °C
Heating Rate 5.00 °Cmin^-1
Baseline Type line
Result Mode Sample Temp
Left Area 66.83 %
Right Area 33.17 %
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normalized 1227.74 Jg^-1
Onset 292.27 °C
Peak Height 5.44 mW
Peak 306.67 °C
Extrapol. Peak 308.38 °C
Endset 311.94 °C
Peak Width 62.09 °C
Left Limit 254.11 °C
Right Limit 395.04 °C
Left bl Limit 254.11 °C
Right bl Limit 395.04 °C
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Result Mode Sample Temp
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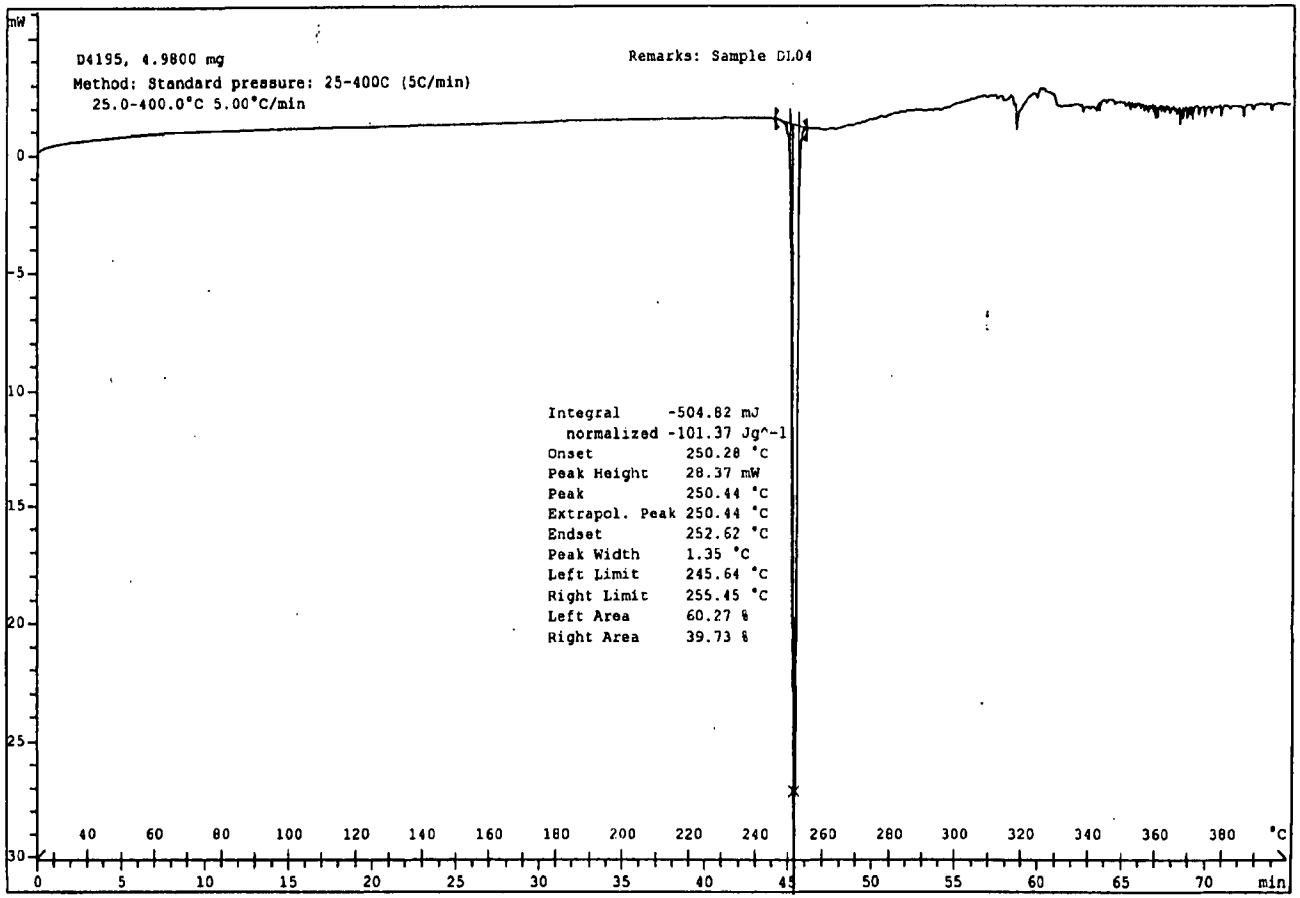
Right Area 66.34 %

Figure 4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D4195, 4.9800 mg
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Remarks: Sample DL04
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normalized -101.37 Jg^-1
Onset 250.28 °C
Peak Height 28.37 mW
Peak 250.44 °C
Extrapol. Peak 250.44 °C
Endset 252.62 °C
Peak Width 1.35 °C
Left Limit 245.64 °C
Right Limit 255.45 °C
Left Area 60.27 %
Right Area 39.73 %
0
5
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40 60 80 100 120 140 160 180 200 220 240 260 280 300 320 340 360 380 °C
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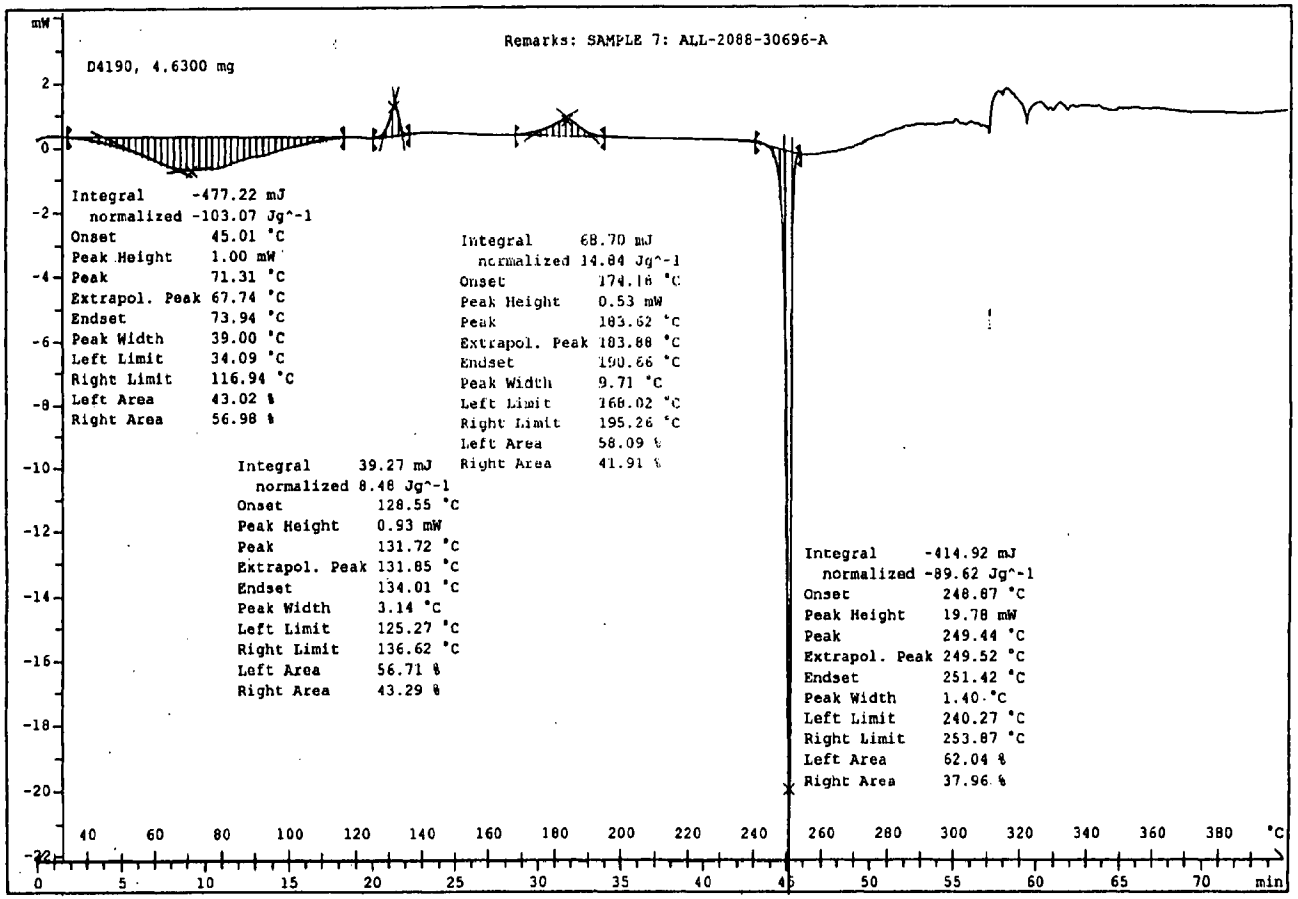
Figure 5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Peak 71.31 °C
Extrapol. Peak 67.74 °C
Endset 73.94 °C
Peak Width 39.00 °C
Left Limit 34.09 °C
Right Limit 116.94 °C
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Right Area 56.98 %
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normalized 14.84 Jg^-1
Onset 174.18 °C
Peak Height 0.53 mW
Peak 183.62 °C
Extrapol. Peak 183.88 °C
Endset 190.66 °C
Peak Width 9.71 °C
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Right Limit 195.26 °C
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Right Area 41.91 %
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Right Area 37.96 %
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Figure 6

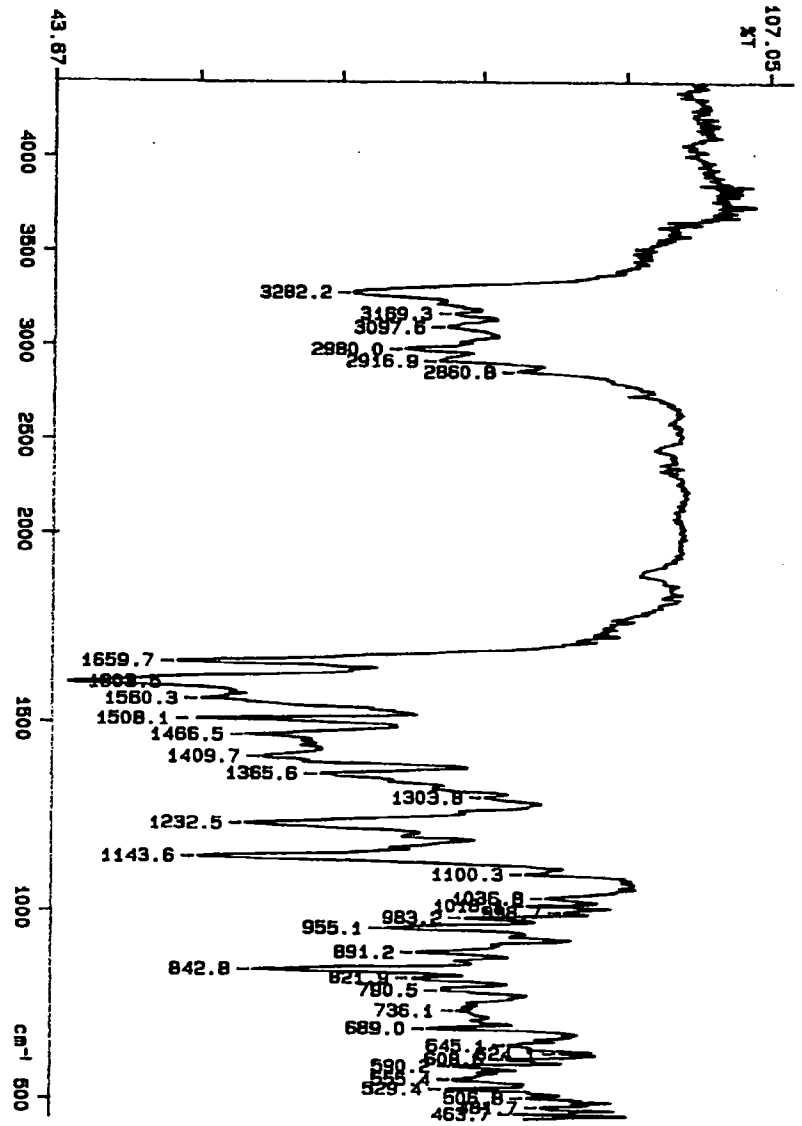
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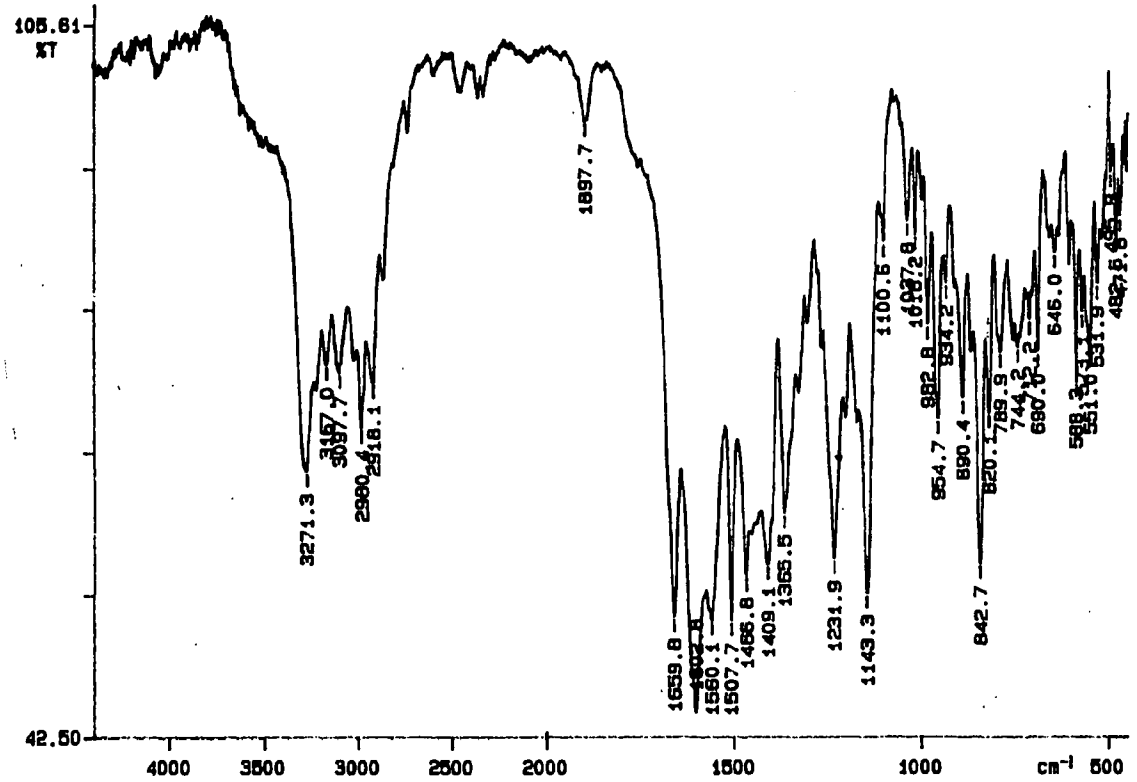
Figure 7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1409.1
1365.5
1231.9
1143.3
1100.5
1037.8
982.8
954.7
890.4
842.7
820.1
789.9
744.2
690.0
646.0
598.3
551.9
531.9

Figure 8

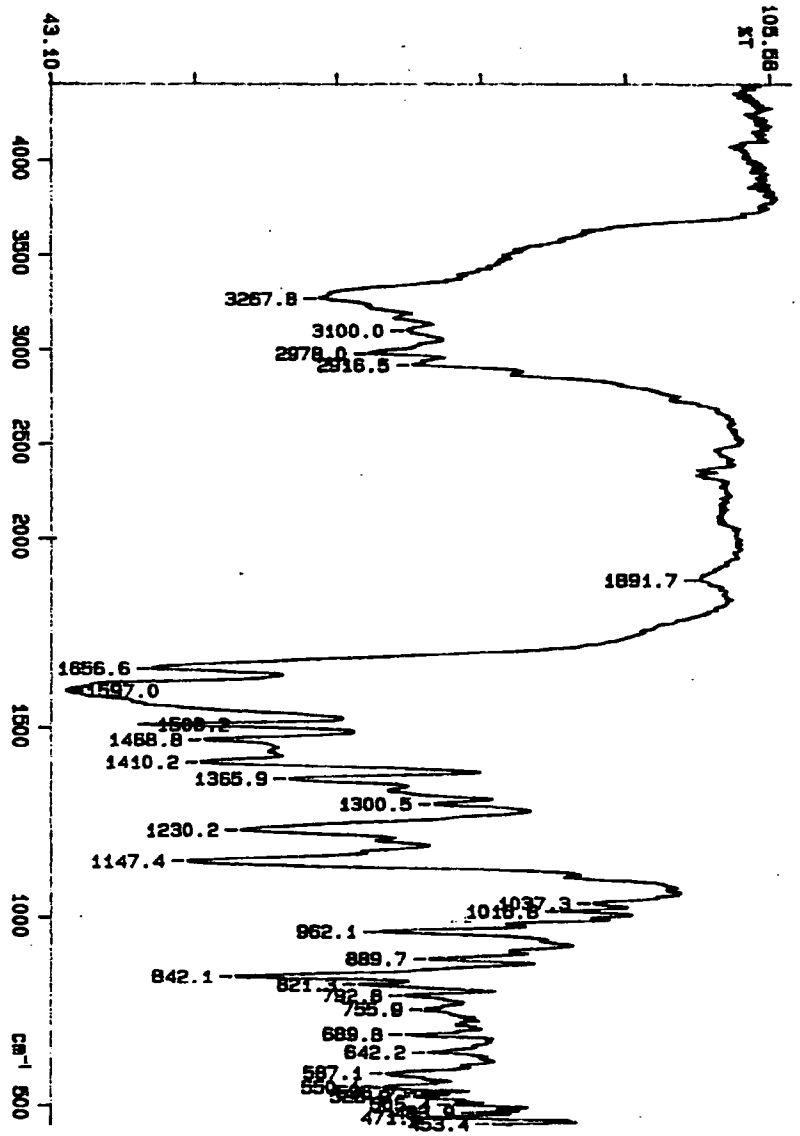
105.58
%T
43.10
4000
3500
3000
2500
2000
1500
1000
500
cm-1
3267.8
3100.0
2978.0
2916.5
1891.7
1656.6
1597.0
1468.8
1410.2
1365.9
1300.5
1230.2
1147.4
1037.3
962.1
889.7
842.1
755.9
689.8
642.2
587.1

Figure 9